

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
4 March 2004 (04.03.2004)

PCT

(10) International Publication Number
WO 2004/018515 A3

(51) International Patent Classification⁷: C07K 14/505, C12N 15/12, A61K 38/18, G01N 33/68

(21) International Application Number:
PCT/EP2003/008725

(22) International Filing Date: 7 August 2003 (07.08.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02017914.9 9 August 2002 (09.08.2002) EP

(71) Applicant (for all designated States except US): MERCK PATENT GMBH [DE/DE]; Frankfurter Strasse 250, 64293 Darmstadt (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BAKER, Matthew [GB/GB]; 8 Saffron Close, Littleport, Ely, Cambridgeshire GB6 1HR (GB). CARR, Francis, J. [GB/GB]; Birchlea, The Holdings, Balmedie, Aberdeenshire AB23 8XU (GB).

(74) Common Representative: MERCK PATENT GMBH; Frankfurter Strasse 250, 64293 Darmstadt (DE).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
3 June 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/018515 A3

(54) Title: T-CELL EPITOPES IN ERYTHROPOIETIN

(57) Abstract: The invention relates to the identification of epitopes for T-cells in human EPO as well as T-cell epitope peptides derived from EPO by means of which it is possible to create novel modified EPO variants with reduced immunogenicity.

INTERNATIONAL SEARCH REPORT

International Application No

EP 03/08725

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/505 C12N15/12 A61K38/18 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K C12N G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, SEQUENCE SEARCH, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 34317 A (ADAIR FIONA SUZANNE ; CARR FRANCIS JOSEPH (GB); HAMILTON ANITA ANNE) 15 June 2000 (2000-06-15) cited in the application page 8 -page 9; claims 14, 21-23 ---	1-5, 8-10, 16-20
X	EP 0 357 804 A (GENETICS INST) 14 March 1990 (1990-03-14) cited in the application column 3; claims 1-9 ---	1-5, 8-10, 16-18
X	EP 0 410 246 A (BEHRINGWERKE AG) 30 January 1991 (1991-01-30) EPO-Peptide P1; page 2, line 50 -page 4, line 26; claims 15-17 ---	11-15, 18 -/-

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the International filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the International search

Date of mailing of the International search report

5 April 2004

19 APR 2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Schmidt, Harald

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08725

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 539 167 A (ORTHO PHARMA CORP) 28 April 1993 (1993-04-28) the whole document ----	
A	EP 1 013 288 A (PFIZER PROD INC) 28 June 2000 (2000-06-28) page 2 -page 3; figures 1-3 ----	
A	EP 0 267 678 A (INTEGRATED GENETICS INC) 18 May 1988 (1988-05-18) pages 2 and 9; figure 4 ----	
A	WO 02 20034 A (BRADBURN JAMES A ; HUNTER CHRISTIE L (US); BOTTI PAOLO (US); CHEN) 14 March 2002 (2002-03-14) Segment SEP-3:4; page 54, line 27 -page 56; example 5 ----	
P, X	WO 02 062843 A (MERCK PATENT GMBH ; CARTER GRAHAM (GB); JONES TIM (GB); CARR FRANCI) 15 August 2002 (2002-08-15) cited in the application the whole document ----	1-10, 16-20
P, X	WO 02 069232 A (MERCK PATENT GMBH ; CARTER GRAHAM (GB); JONES TIM (GB); CARR FRANCI) 6 September 2002 (2002-09-06) page 1 -page 11; claims 1,2; example 7 ----	1-10, 16-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/08725

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 1-6, 8-10, 16-18 (all partially) because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-6,8-10,16-18 (all partially)

Present claims 1-5,8-10 and 16-18 relate to a compound defined by reference to a desirable property, namely having the biological activity of human EPO and being substantially non-immunogenic or less immunogenic than any non-modified EPO molecule.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved.

Moreover, present claims 1-5,8-10 and 16-18 relate to a compound defined (*inter alia*) by reference to the parameter "stimulation index". The use of this parameter in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible.

Furthermore, it is completely unclear in the sense of Article 6 PCT how the following disclaimer is to be understood: "and whereby simultaneously X1=I, X2=L, X3=W, X4=L, X5=L, X6=V, X7=I, X8=F, X9=V, X10=Y, X11=F, X12=L, and X13=L are excluded" (see claim 6). These amino acids are not comprised in the definitions for X1 to X13 in the characterizing part of claim 6, rendering the scope of claims 6 and 8-10 unclear.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the molecules having an amino acid sequence as defined in claim 6 without the disclaimed sequences, and claim 7.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-10,16,17 (completely) and 18 (partially)

Modified molecule having the biological activity of human EPO and being substantially non-immunogenic or less immunogenic than any non-modified molecule, DNA coding for such a protein and pharmaceutical composition comprising modified EPO molecules

2. Claims: 11-15,19,20 (completely) and 18 (partially)

Peptide sequence being part of a molecule having the biological activity of human EPO and comprising one or more T-cell epitopes being MHC class II ligands and DNA coding for such a peptide; method of constructing a T-cell epitope map of human EPO by locating T-cell epitopes in human EPO

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

EP 03/08725

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0034317	A 15-06-2000	AU 1667600 A CA 2342967 A1 CN 1294596 T EP 1051432 A2 WO 0034317 A2 JP 2002534959 T AU 4635699 A		26-06-2000 15-06-2000 09-05-2001 15-11-2000 15-06-2000 22-10-2002 24-01-2000
EP 0357804	A 14-03-1990	US 4835260 A EP 0357804 A1		30-05-1989 14-03-1990
EP 0410246	A 30-01-1991	DE 3924746 A1 AT 161577 T AU 648506 B2 AU 5977890 A CA 2021912 A1 DE 59010787 D1 DK 410246 T3 EP 0410246 A1 ES 2111524 T3 GR 3026096 T3 IE 902707 A1 JP 3081294 A JP 3155002 B2 KR 175657 B1 PT 94813 A ,B US 5712370 A US 5106954 A		31-01-1991 15-01-1998 28-04-1994 31-01-1991 27-01-1991 05-02-1998 31-08-1998 30-01-1991 16-03-1998 29-05-1998 27-02-1991 05-04-1991 09-04-2001 01-04-1999 20-03-1991 27-01-1998 21-04-1992
EP 0539167	A 28-04-1993	AU 668841 B2 AU 1168495 A AU 658231 B2 AU 2718392 A CA 2080891 A1 EP 0539167 A2 FI 924747 A JP 3342060 B2 JP 5214092 A JP 2003012697 A KR 233777 B1 NO 924060 A NO 971085 A NZ 244778 A ZA 9208099 A		16-05-1996 01-06-1995 06-04-1995 22-04-1993 22-04-1993 28-04-1993 22-04-1993 05-11-2002 24-08-1993 15-01-2003 01-12-1999 22-04-1993 22-04-1993 25-03-1994 20-04-1994
EP 1013288	A 28-06-2000	AU 5956099 A CA 2288341 A1 CN 1265921 A EP 1013288 A2 JP 2000178207 A NZ 501193 A ZA 9907266 A		22-06-2000 17-06-2000 13-09-2000 28-06-2000 27-06-2000 29-06-2001 23-05-2001
EP 0267678	A 18-05-1988	US 4954437 A AU 7842987 A DK 478287 A EP 0267678 A1 FI 873897 A		04-09-1990 16-03-1989 16-03-1988 18-05-1988 16-03-1988

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

R/EP 03/08725

Patent document cited in search report	Publication date		Patent family member(s)	Publication date	
EP 0267678	A	JP PT	63185396 A 85699 A ,B	30-07-1988 01-10-1987	
WO 0220034	A	14-03-2002	AU AU AU AU BG BR CA CA CA CA CN CN CN CN CN CZ EP EP EP EP HU NO NO NO SK WO WO WO WO US	7338501 A 7338801 A 7890501 A 8893701 A 107590 A 0113579 A 2412277 A1 2412278 A1 2412279 A1 2412298 A1 1457257 T 1452632 T 1454097 T 1458846 T 20030678 A3 1318827 A1 1315513 A2 1315511 A2 1315738 A1 0303854 A2 20031047 A 20031048 A 20031049 A 2772003 A3 0219963 A2 0220033 A1 0220034 A1 0220557 A1 2003191291 A1	22-03-2002 22-03-2002 22-03-2002 22-03-2002 31-12-2003 17-06-2003 14-03-2002 14-03-2002 14-03-2002 19-11-2003 29-10-2003 05-11-2003 26-11-2003 17-03-2004 18-06-2003 04-06-2003 04-06-2003 04-06-2003 01-03-2004 08-05-2003 08-05-2003 08-05-2003 07-10-2003 14-03-2002 14-03-2002 14-03-2002 14-03-2002 09-10-2003
WO 02062843	A	15-08-2002	CA WO EP BR BR BR BR BR CA CA CA CA CA CA CA CA CA CA CA WO WO WO WO WO WO WO WO EP EP EP	2437272 A1 02062843 A2 1357933 A2 0207014 A 0207016 A 0207017 A 0207018 A 0207281 A 2437214 A1 2437263 A1 2437265 A1 2437270 A1 2437287 A1 2438513 A1 2438652 A1 02062832 A2 02062375 A1 02077034 A2 02062842 A1 02062833 A2 02066058 A1 02069232 A2 1360200 A2 1357934 A1 1360201 A1	15-08-2002 15-08-2002 05-11-2003 25-02-2004 03-02-2004 03-02-2004 10-02-2004 15-08-2002 15-08-2002 15-08-2002 15-08-2002 03-10-2002 29-08-2002 06-09-2002 15-08-2002 15-08-2002 03-10-2002 15-08-2002 15-08-2002 15-08-2002 29-08-2002 06-09-2002 12-11-2003 05-11-2003 12-11-2003

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/08725

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 02062843	A	EP	1361893 A1	19-11-2003
		EP	1387856 A2	11-02-2004
		EP	1366455 A2	03-12-2003
		EP	1392731 A2	03-03-2004
		HU	0303150 A2	29-12-2003
		HU	0303173 A2	29-12-2003
		HU	0303199 A2	29-12-2003
WO 02069232	A 06-09-2002	BR	0207014 A	25-02-2004
		BR	0207016 A	03-02-2004
		BR	0207017 A	03-02-2004
		BR	0207018 A	03-02-2004
		BR	0207281 A	10-02-2004
		CA	2437214 A1	15-08-2002
		CA	2437263 A1	15-08-2002
		CA	2437265 A1	15-08-2002
		CA	2437270 A1	15-08-2002
		CA	2437272 A1	15-08-2002
		CA	2437287 A1	03-10-2002
		CA	2438513 A1	29-08-2002
		CA	2438652 A1	06-09-2002
		WO	02062832 A2	15-08-2002
		WO	02062375 A1	15-08-2002
		WO	02077034 A2	03-10-2002
		WO	02062843 A2	15-08-2002
		WO	02062842 A1	15-08-2002
		WO	02062833 A2	15-08-2002
		WO	02066058 A1	29-08-2002
		WO	02069232 A2	06-09-2002
		EP	1360200 A2	12-11-2003
		EP	1357934 A1	05-11-2003
		EP	1360201 A1	12-11-2003
		EP	1361893 A1	19-11-2003
		EP	1357933 A2	05-11-2003
		EP	1387856 A2	11-02-2004
		EP	1366455 A2	03-12-2003
		EP	1392731 A2	03-03-2004
		HU	0303150 A2	29-12-2003
		HU	0303173 A2	29-12-2003
		HU	0303199 A2	29-12-2003

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
4 March 2004 (04.03.2004)

PCT

(10) International Publication Number
WO 2004/018515 A2

(51) International Patent Classification⁷: C07K 14/505, (74) Common Representative: MERCK PATENT GMBH;
C12N 15/12, A61K 38/18 Frankfurter Strasse 250, 64293 Darmstadt (DE).

(21) International Application Number:
PCT/EP2003/008725

(22) International Filing Date: 7 August 2003 (07.08.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02017914.9 9 August 2002 (09.08.2002) EP

(71) Applicant (for all designated States except US): MERCK PATENT GMBH [DE/DE]; Frankfurter Strasse 250, 64293 Darmstadt (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BAKER, Matthew [GB/GB]; 8 Saffron Close, Littleport, Ely, Cambridgeshire GB6 1HR (GB). CARR, Francis, J. [GB/GB]; Birchlea, The Holdings, Balmedie, Aberdeenshire AB23 8XU (GB).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 2004/018515 A2

(54) Title: T-CELL EPITOPES IN ERYTHROPOIETIN

(57) Abstract: The invention relates to the identification of epitopes for T-cells in human EPO as well as T-cell epitope peptides derived from EPO by means of which it is possible to create novel modified EPO variants with reduced immunogenicity.